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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/287,884	04/07/1999	HAROLD J. WANEBO	58463/JPW/EM	6824

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EXAMINER	
LEWIS, AMY A	
ART UNIT	**PAPER NUMBER**
1614	

DATE MAILED: 11/14/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/287,884	WANEBO ET AL.	
	Examiner	Art Unit	
	Amy A. Lewis	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 July 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Case

The Amendment, filed 29 July 2005, has been entered into the application. Accordingly, claim 29 has been amended, and claims 1-19 have been cancelled.

Claims 20-33, as filed 29 July 2005, are pending.

Response to Applicants Arguments, filed 29 July 2005:

1) The rejection of claims 20 and 21 under 35 USC 102(a) as being anticipated by Myrick et al. (1997 *FASB Journal*, Vol. 11(2), p. A546 (abstract 3157)) has been withdrawn in view of the 1.132 Declaration, filed 29 July 2005.

2) The rejection of claims 20, 22-25, and 27-31 under 35 USC 102(e) as being anticipated by Joshi (US Patent No. 6,841,537) is *withdrawn* in view of Applicant's argument that the reference is directed to ceramide and not C_6-ceramide.

3) The rejection of claims 20, 25, 26, 30, and 31-33 as being unpatentable over Jayadev et al., (1995 *J biological Chemistry* 270(5): pages 2047-2052), in view of Myceck et al, US Patent Nos. 5,597,830 and 6147,060, is *maintained* for the reasons of record and further below.

In response to Applicant's argument that the Examiner has failed to establish a *prima facie* case of obviousness against the rejected claims, the following case law is believed to be relevant to the instant claim rejections and argument:

In re Kerkhoven (205 USPQ 1069, CCPA 1980) states that "It is *prima facie* obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the same purpose: the idea of combining them flows logically from their having been individually taught in the prior art." Therefore, it would have been obvious to a person of ordinary skill in the are at the time the invention was made to combine C_6-ceramide and paclitaxel, motivated by their having been taught by the prior art to be useful in treating the claimed cancer types, consonant with the reasoning of the cited case law.

New/Modified Grounds of Rejection:

The text of those sections of Title 35, U. S. Code not included in this action can be found in a prior Office Action. THis can be used in second and subsequent nonfinals where the statute was recited in a prior office action.

Claim Rejections - 35 USC § 103

1) Claims 20, 22-25, and 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Joshi (US Patent No. 6,841,537) in view of Hartfield PJ et al., "Ceramide induces apoptosis in PC12 cells," 1997 *FEBS Letters* Vol. 401, pages 148-152.

Joshi et al. teaches a method of cancer therapy where the cancer cells are transformed with nucleic acids that encode gene products to inhibit growth of the cancer cells (abstract). The method includes administering to a cancer patient a nucleic acid (also referred to as a foreign

therapeutic gene) that transforms the cancer cells and inhibits their growth by inducing apoptosis; and further administering paclitaxel as a cell cycle synchronizer to enhance the effect of the foreign therapeutic gene ('537 claims 1, 8, 9, 15, 16, 22, and 23).

Specific claim limitations are addressed below in subsections 2a-2c:

2a) In addition, the paclitaxel is in a liposomal formulation of instant claims 23 and 29, of which ceramide is listed as an example (specification col. 7, line 64; claims 9 and 23).

2b) Joshi et al. teach the administration techniques of instant claims 24 and 29 at col. 16, lines 60+ of the specification, including intravenous injection.

2c) Joshi et al. teach the treatment of human colon adenocarcinoma, human ovarian carcinoma, mouse melanoma, lung carcinoma, of the Markush groups of claims 20, 25, 30, and 31 (specification col. 16 lines 30-56, Table 1).

Joshi does not teach C_6-ceramide specifically.

Hartfield teaches that C_6-ceramide induces apoptosis in PC12 cells (an adrenal tumor cell line) (See: abstract; p. 150, Fig. 2). The reference also teaches that ceramide, C_6-ceramide, and C_2-ceramide have the same efficacy for inducing apoptosis (See Fig. 2A).

The substitution of C_6-ceramide (from the Hartfield reference) for the ceramide in the method disclosed by Joshi would have been obvious because Hartfield teaches that C_6-ceramide and ceramide have the same efficacy for inducing apoptosis in PC12 cells. Therefore, these may be considered to be art-accepted equivalents.

One of skill in the art would have been motivated at the time of invention to make this substitution in order to obtain the method of inducing apoptosis in cancer cells as suggested by

the references with a reasonable expectation of success, with both ceramide and C_6-ceramide having been taught to have the same efficacy for inducing apoptosis. The claimed subject matter fails to patentably distinguish over the state of the art as represented by the cited references. Therefore, the claims are properly rejected under 35 U.S.C. § 103.

2) Claims 20-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Spencer CM and Faulds D ("Paclitaxel. A review of its pharmacodynamic and pharmacokinetic properties and therapeutic potential in the treatment of cancer," 1994 *Drugs* 48(5): 794-847), in view of Cai Z et al. ("Alteration of the sphingomyelin/ceramide pathway is associated with resistance of human breast carcinoma MCF7 cells to tumor necrosis factor-alpha-mediated cytotoxicity," 1997 *J Biological Chemistry* 272(11): 6918-6926).

Spencer teaches that paclitaxel has *in vitro* as well as *in vivo* toxicity against several human cancer cell lines, including, breast carcinoma, metastatic breast cancer, cervical cancer, colon carcinoma, endometrial carcinoma, glioma, head and neck squamous cell carcinoma, leukaemia, neuroblastoma, non-small cell lung cancer, ovarian carcinoma, pancreatic carcinoma, prostate cancer, small cell lung cancer, non-Hodgkin's lymphoma, and multiple myeloma. (See: abstract; Table 1 on p. 804). The reference also reviews paclitaxel therapy in phase I and II trials in patients with advanced breast cancer, advanced ovarian cancer, metastatic head and neck squamous cell carcinoma, non-small cell lung cancer, small cell lung cancer, non-Hodgkins lymphoma (see: p. 798-799, 806-807).

Regarding claims 23 and 28 drawn to the cremophore formulation, Spencer teaches that paclitaxel is poorly soluble in water; therefore it is formulated in a vehicle of 50%

polyoxyethylated castor oil (i.e., the common name for "Cremophore"; see BASF reference, cited for definition purposes) and 50% alcohol (ethanol). (See: Spencer p. 800).

Spencer also teaches combination therapy with paclitaxel and several other agents, such as cisplatin, cyclophosphamide, doxorubicin, hydroxyurea, and dexamethasone (p. 798-799, 805-806, 821-826). The reference teaches that the effectiveness could be additive or synergistic (greater than additive). For example, the effect was greater than additive in ovarian cancer cells when paclitaxel was administered prior to cisplatin; the effect was additive in human lung or breast cancer cells (p. 806, 821-826).

The Spencer reference does not teach combination therapy with C_6-ceramide.

Cai teaches that C_6-ceramide kills both TNF-sensitive and TNF-resistant MCF7 cells through apoptosis (See: p. 6922-6923, Fig. 5). The secondary reference does not teach paclitaxel.

It would have been obvious to a person of ordinary skill in the art at the time the invention was made to use a combination of paclitaxel and C_6-ceramide to treat breast carcinoma, metastatic breast cancer, cervical cancer, colon carcinoma, endometrial carcinoma, glioma, head and neck squamous cell carcinoma, leukaemia, neuroblastoma, non-small cell lung cancer, ovarian carcinoma, pancreatic carcinoma, prostate cancer, small cell lung cancer, non-Hodgkin's lymphoma, and multiple myeloma. The skilled artisan would have been motivated to combine paclitaxel and C_6-ceramide, and would have had a reasonable expectation of success, having been taught by the prior art (Spencer) that it is known to use paclitaxel combination with conventional cancer treatments. The skilled artisan would have additionally been motivated to use a combination of paclitaxel and C_6-ceramide having been taught by the prior art that

paclitaxel in combination with other anti-cancer agents is known to show additive and/or greater than additive effects against various cancers (such as ovarian, breast, and lung cancer). Therefore, the invention as a whole would have been prima facie obvious.

Claim Rejections - 35 USC § 112, 1st paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 20-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of increasing apoptosis in leukemia (in Jurkat cells), breast cancer (in the cell lines MCF7), prostate cancer (in the cell line LnCap), colon cancer (in the cell line HT29), pancreatic cancer (in the cell line RWP-2), and head and neck squamous cell carcinoma (in the cell line TU-138) (See specification pages: 51-52 and Table 2; 33-38 and Fig. 6; 60-66; Figs. 2, 9, 11 and 12) with the combination of paclitaxel and C_6-ceramide, does not reasonably provide enablement for increasing apoptosis in all cancer types listed in the Markush group of claims 20, 25, 30 and 31 of cancer cells or all types of tumor growth *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Attention is directed to *In re Wands*, 8 USPQ2d 1400 (CAFC 1988) at 1404 where the court set forth the eight factors to consider when assessing if a disclosure would have required

undue experimentation. Citing *Ex parte Forman*, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

1) Nature of the invention.
2) State of the prior art.
3) Relative skill of those in the art.
4) Level of predictability in the art.
5) Amount of direction or guidance provided by the inventor.
6) Presence or absence of working examples.
7) Breadth of the claims.
8) Quantity of experimentation necessary to make or use the invention based on the content of the disclosure.

The instant specification fails to provide guidance that would allow the skilled artisan to practice the instant invention without resorting to undue experimentation, as discussed in the subsections set forth hereinbelow.

1) The nature of the invention.

The claimed invention relates generally to chemotherapy, and specifically to compositions and methods for inhibiting the proliferation of cancer cells and tumor growth without regard to the environment (see instant claim 20 for example) which includes both *in vitro* and *in vivo*.

2) State of the prior art.

While the state of the art is relatively high with regard to the treatment of specific cancer types, the state of the art with regard to treating cancer broadly is underdeveloped. In particular, there is no known anticancer agent that is effective against all cancer cell types. The Cecil reference (Textbook of Medicine, 21st Edition (2000), Goldman & Bennett (Editors), W.B. Saunders Company (Publisher), Chapter 198, pages 1060-1074) clearly shows that for the various known cancer types, there is no one specific

chemotherapeutic agent that is effective for all types of cancer (see page Table 198-5 at page 1065; Tables 198-6 and 198-7 at page 1066; Table 198-8 at page 1068; and Table 198-9 at page 1071).

3) Relative skill of those in the art.

The relative skill of those in the art is high, generally that of a PHD/MD with several years of practical experience.

4) Level of predictability in the art.

The cancer treatment art involves a very high level of unpredictability as demonstrated by the state-of-the-art with regard to the treatment of specific cancers with specific agents and has long been underdeveloped with regard to the treatment of cancers broadly (see discussion in section *2)* above on the state of the prior art). The lack of significant guidance from the present specification or prior art with regard to the actual treatment of all types of cancer cells in a mammal, including a human subject, with the claimed active ingredients makes practicing the claimed invention unpredictable.

Furthermore, the unpredictability observed with single agents is compounded where synergistic performance is sought. This is summarized by USP 6,664,288 at col. 1, lines 28-37:

> Combination therapies, while desirable, are a hit or miss proposition. The treatments are typically not additive. In many cases, cross effects and treatment load can result in lower effectiveness for the combinations, than either treatment alone. Problems encountered include multiple drug resistance (MDR), where the malignant cell in essence pumps the cytotoxic compounds and other compounds out of the cell, thereby preventing continued useful treatment of the cancer.

This is verified by U.S. Pat. 6,465,448 at col. 1, lines 56-59:

> The design of drug combinations for the chemotherapeutic treatment of cancer should be approached with the goals of 1) finding a combination that is synergistic with and not merely additive to the first compound with respect to the elimination of the tumor, and 2) finding a second drug that does not potentiate the toxic effects of the first therapeutic agent. *These conditions require a great deal of empirical testing* of agents known to have anticancer properties with agents that either may have anticancer properties, or that may augment the first agent in other ways. (Emphasis added).

Thus, when two (or more) agents are sought to be used synergistically, even more additional empirical testing is required, again with no *a priori* expectation of success.

5) Amount of direction or guidance provided by the inventor & 6) Presence or absence of working examples.

The specification teach the specific treatment of leukemia (in Jurkat cells), breast cancer (in the cell lines MCF7), prostate cancer (in the cell line LnCap), colon cancer (in the cell line HT29), pancreatic cancer (in the cell line RWP-2), and head and neck squamous cell carcinoma (in the cell line TU-138) with paclitaxel and C_6-ceramide. The specification also teaches treatment (in *in vivo* mouse tumor models) for head and neck squamous cell carcinoma (see p. 33-38 and Fig 6). The specification discusses an *in vivo* experiment which evaluates treatment of breast cancer cells MCF-7 with paclitaxel and C_6-ceramide, however it does not describe the results of this experimehnt (see p. 66). The specification does not teach paclitaxel and C_6-ceramide or demonstrate a greater than additive increase in apoptosis for any other cancer types.

7) Breadth of claims.

The claims are very broad and inclusive of a broad range of cancer types. The

breadth of the claims exacerbate the complex nature of the subject matter to which the present claims are directed.

8) Quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification does not enable any person skilled in the art to which it pertains (i.e. chemotherapy and treatment of cancer) to make or use the invention commensurate in scope with the claims. The lack of adequate guidance from the specification or prior art with regard to the actual treatment of all claimed cancers with paclitaxel in combination with C_6-ceramide fails to rebut the presumption of unpredictability existent in this art (See Remarks filed 7 April 1999, p. 11). Applicants fail to provide the guidance and information required to treat all claimed caner types with the claimed combination of paclitaxel and C_6-ceramide without resorting to undue experimentation.

Absent a reasonable *a priori* expectation of success for using a specific chemotherapeutic agent/combination to treat any particular type of cancer, one skilled in the art would have to extensively test many various tumor types. Since each prospective embodiment, and indeed future embodiments as the art progresses, would have to be empirically tested, and those which initially failed tested further, an undue amount of experimentation would be required to practice the invention as its is claimed in its current scope, because the specification provides inadequate guidance to do otherwise.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 23 and 28 contain the trade name "cremophore." M.P.E.P. § 2173.05(u) recites, "It is important to recognize that a trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus a trademark or trade name does not identify or describe the goods associated with the trademark or trade name." If the trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. § 112, second paragraph. *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982).

Summary

This action is made NON-FINAL. Claims 20-33 are rejected. No claims are allowed.

Contact Information:

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy A. Lewis whose telephone number is (571) 272-2765. The examiner can normally be reached on Monday-Friday, 9:00-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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